REMARKS

Reconsideration of the rejections is respectfully requested.

Assuming entry of the amendment, the status of the claims is as follows:

Amended:	1, 13
Cancelled:	2
New:	None
Pending:	1, 3-13
Allowed:	None

Claims

Claims 1-13 were pending. Claims 1-13 stand rejected.

It is believed that entry of this Amendment is timely filed with the payment of a 1 month extension of time. Notwithstanding, Applicants hereby authorize the Commissioner to charge any additional claim fees required by entry of this Amendment to Deposit Account No. 04-0480.

Claim 2 has been cancelled.

Claim Rejection under 35 U.S.C. §112, second paragraph

The Examiner has rejected Claim 13 based on 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Specifically, the Examiner asserts that, in Claim 13, "the phrase 'stamp-like' renders the claim indefinite because the claim includes elements not actually disclosed (those encompassed by 'stamp-like'), thereby rendering the scope of the claim unascertainable."

Applicants respectfully disagree. In the specification (see page 6, line 17 through page 7, line 1), Applicants state that a "core," containing the electrostatically deposited active ingredient, may be further processed into dosage forms comprising "non-conventional wafers or stamp-like presentations," and that such preferred forms are disclosed in published international patent application number WO 99/63972, which is incorporated by reference. In particular, this publication discloses "postage-stamp" dosage forms (see page 43, line 31 through page 44, line 2) and are disclosed in Figures 45a and 45b of WO 99/63972. WO 99/63972 is of record in this case. *See* Specification, page 6, lines 16-18.

The rejection, it is respectfully submitted, should be withdrawn.

Claim Rejection under 35 U.S.C. §103(a)

Claims 1-13 stand rejected under 35 U.S.C. §103(a), based on an assertion that the subject matter of the claims was unpatentable over Pletcher et al. (U.S. Pat. No. 6,074,688)("Pletcher") in view of Chen et al. (U.S. Pat. No. 5,225,204)("Chen")[2] and Rudnic et al. (U.S. Pat. No. 5,430,021)("Rudnic"). Applicants respectfully disagree. Applicants submit that the Office's rejection of Claims 1-13 under §103(a) should be withdrawn because (A) the Office used hindsight reconstruction in its combination of Pletcher, Chen, and Rudnic, which is an improper basis for rejection, and (B) the combination of these three references actually teaches away from the present invention.

A. *The Office's Use of Hindsight Reconstruction to Reject Claims 1-13 Under 35 U.S.C. §103(a) is Improper and Should be Withdrawn.*

An analysis of the Office's reasoning behind its rejection under 35 U.S.C. §103(a) reveals one basic flaw. To be obvious, it is not enough for claim elements A, B, and C to be in the art. Instead, the art must *suggest their combination*, and *the desirability of their combination*. Here, the Office used hindsight reconstruction to put these features together. Such use of hindsight reconstruction is improper.

The Court of Appeals for the Federal Circuit has repeatedly held that to support a rejection under §103(a), the references must suggest the desirability of modification of the cited documents to produce the claimed invention. MPEP §2143.01; see also In re Lawkowski, 871 F.2d 115, 117, 10 USPQ2d 1397, 1398 (Fed. Cir. 1989) (the "mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification"); Northern Telecom, Inc. v. Datapoint Corp., 908 F.2d 931, 934, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). Thus, the standard for the proper combination of references to form a rejection under 35 U.S.C. §103(a) requires that the teaching of the *desirability* of combining the references be found in the cited art. Northern Telecom, Inc. v.

[2] It should be noted that, in the body of the Office Action, Chen is identified by an incorrect patent number, U.S. Pat. No. 5,225,294. The correct patent number for Chen is U.S. Pat. No. 5,225,204.

Datapoint Corp., 908 F.2d at 934 ("It is insufficient that the prior art disclosed the components of the patented device, either separately or used in other combinations; there must be some teaching, suggestion or incentive to make the combination made by the inventor.") Applicants assert that the Office has given no indication of why the combination of these references would be desirable - thus, the rejection was improper.

The present invention involves the electrostatic deposition of a thyroid hormone onto a pharmaceutically acceptable polymer substrate. The thyroid hormone is deposited as a dry powder, substantially free of excipients. The Examiner is correct that Pletcher et al. ("Pletcher") discloses a method for electrostatically binding a powdered medicament to a substrate. Moreover, the Examiner acknowledges that "[t]hough Pletcher discloses the method and substrate of the claimed invention, it does not specifically disclose or suggest the nature of the powdered medicament used, specifically the ... variety of medicament." Thus, in order to arrive at the present invention, the Examiner seeks to combine Pletcher with the teachings of Rudnic et al. ("Rudnic") and Chen et al. ("Chen"). However, there is no motivation in the art for combining Pletcher, Rudnic and Chen. In any case, such a combination neither teaches nor suggests the present invention.

Rudnic discloses hydrophobic carrier systems in which a drug, which may include thyroid releasing hormone (TRH), is formed into particles after first mixing the drug with a hydrophobic material selected from long chain carboxylic acids, long chain carboxylic acid esters and long chain carboxylic acid alcohols. *See* Rudnic at col.1, line 66 – col. 2, line 2; col. 3, lines 13-22, 32-37 and 45-47. Thus, the particles of Rudnic are not "substantially free of excipients," as required by the pending claims, but are the product of an admixture with a hydrophobic carrier excipient. It also must be noted that Rudnic is wholly inapposite to claims 3 and 9, which limit the thyroid hormone to levothyroxine sodium or triiodothyronine – neither of which is taught or suggested by Rudnic's TRH.

Chen, similarly, does not disclose deposition of "a dry powder substantially free of excipients," as required by the claims. Chen discloses the use of polyvinylpyrrolidone or Poloxamer as a stabilizing complexing agent for levothyroxine sodium. Once mixed with such a complexing agent (excipient), the levothyroxine sodium is "granulated with a polar organic solvent and uniformly adsorbed on a cellulose compound." *See* Chen at col. 3, lines 23-29. Although Chen also discloses that, as an alternative, "the levothyroxine sodium may be at least

partially solubilized directly in the solvent without a complexing agent," *see* Chen at col. 5, lines 60-66, emphasis added, this use of a solvent is not "electrostatically depositing...a dry powder," as required by the claims. Moreover, Chen teaches that such an alternative approach is not preferred (note Chen's use of the word "partially," above), because "[a]lthough levothyroxine sodium has relatively limited solubility in water and in other polar organic solvents, the use of a complexing agent which is soluble in these solvents helps to solubilize the levothyroxine sodium." *See* Chen at col. 4, lines 21-25.

Thus, neither Rudnic nor Chen teaches or suggests the electrostatic deposition of a dry powder active ingredient, substantially free of excipients. There would be no motivation to combine either of these references with Pletcher, which merely enables a method of electrostatic deposition. Instead, the Office used hindsight reconstruction to combine these three references. This was improper and the rejection, it is respectfully submitted, should be withdrawn.

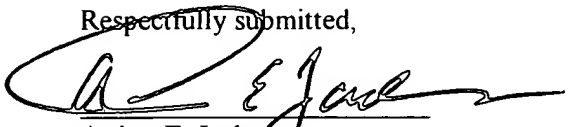
B. *The Office's Rejection on the Basis of 35 U.S.C. §103(a) was Improper Because a Combination of the Cited References Teaches Away From the Present Invention.*

The present invention claims both a method of formulating a solid dosage of thyroid hormone and a solid pharmaceutical dosage formulation of the thyroid hormone that is electrostatically deposited as a dry powder "*substantially free of excipients.*" Applicants respectfully submit that, even if the Pletcher, Chen, and Rudnic references were combined, the result would be an electrostatic deposition of particles *containing* excipients – either the hydrophobic material excipient disclosed in Rudnic or the complexing agent excipient disclosed in Chen. Therefore, such a combination of these three references would teach away from the present invention. The rejection, it is respectfully submitted, should be withdrawn.

Conclusion

In light of the above discussion and amendments, it is respectfully submitted that the claims are in condition for allowance. The issuance of a Notice of Allowance is earnestly solicited.[3]

Respectfully submitted,



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Appendix A1: Pending claims (clean copy)

A1

1. **(Amended)** A method of formulating a solid dosage of thyroid hormone, while avoiding instability caused by interaction of the active ingredient with excipients, comprising electrostatically depositing the active ingredient, as a dry powder substantially free of excipients, onto a pharmaceutically acceptable polymer substrate.

3. **(Unchanged)** The method of claim 1, wherein the thyroid hormone is levothyroxine sodium or triiodothyronine.

4. **(Unchanged)** The method of claim 1, wherein the polymer has received regulatory approval and is of GRAS status.

5. **(Unchanged)** The method of claim 4, wherein the polymer is selected from the group consisting of polyvinyl alcohol, polyvinyl pyrrolidinone, polysaccharide polymers, acrylate polymers, methacrylate polymers, phthalate polymers, polyvinyl acetate, methyl cellulose, carboxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, ethyl cellulose, Eudragits, starch-based polymers, gelatin, and combinations thereof.

6. **(Unchanged)** The method of claim 4, wherein the polymer is substantially unreactive with an amino group or iodo group in the thyroid hormone molecule.

7. **(Unchanged)** The method of claim 6, wherein the polymer is selected from the group consisting of hydroxypropylcellulose, hydroxypropylmethylcellulose, ethyl cellulose and combinations thereof.

8. **(Unchanged)** An improved solid pharmaceutical dosage formulation, comprising a therapeutic amount of thyroid hormone, electrostatically deposited on a

pharmaceutically acceptable polymer substrate as a dry powder substantially free of excipients, wherein the average powder particle size is less than about 15μ.

9. **(Unchanged)** The formulation of claim 8, wherein the thyroid hormone is levothyroxine sodium or triiodothyronine.

10. **(Unchanged)** The formulation of claim 8, wherein the average powder particle size is less than about 10μ.

11. **(Unchanged)** The formulation of claim 8, wherein the average powder particle size is less than about 5μ.

12. **(Unchanged)** The formulation of claim 8, wherein the polymer is substantially unreactive with an amino group or iodo group in the thyroid hormone molecule.

13. **(Amended)** The method of claim 1, further comprising:

(a) applying a cover film to encapsulate the electrostatically deposited active ingredient, so as to form a stable core; and

(b) further processing the stable core into a dosage form resembling a tablet, capsule, caplet, wafer or stamp-like presentation.

A2

Appendix A2: Pending claims (redline copy)

1. **(Amended)** A method of formulating a solid dosage of thyroid hormone, while avoiding instability caused by interaction of the active ingredient with excipients, comprising electrostatically depositing the active ingredient, as a dry powder substantially free of excipients, onto a pharmaceutically acceptable polymer substrate.

13. **(Amended)** The method of claim 1 ~~2~~, further comprising:

(a) applying a cover film to encapsulate the electrostatically deposited active ingredient, so as to form a stable core; and

(b) further processing the stable core into a dosage form resembling a tablet, capsule, caplet, wafer or stamp-like presentation.